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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,020	10/16/2001	Daniel S. Kohane	0492611-0417 (MIT 8966)	5504

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EXAMINER	
FUBARA, BLESSING M	
ART UNIT	**PAPER NUMBER**
1618	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,020	KOHANE ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-65 and 80-85* is/are pending in the application.

4a) Of the above claim(s) *21,22,26,29,31-36 and 38-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6-20, 23-25, 27, 28, 30, 37, 46-65 and 80-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of request for extension of time, request for continued examination filed under 37 CFR 1.114, both filed 1/10/06; amendment and remarks filed after final rejection and entered with the RCE; change of address filed 10/07/05. Claims 1, 2, 6-65 and 80-85 are pending and of these claims, 21, 22, 26, 29, 31-36 and 38-45 are withdrawn from consideration.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 1/10/2006 has been entered.

Claim Rejections - 35 USC § 102

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1, 2, 6, 7, 13, 17-20, 23-25, 27, 28, 30, 37, 46, 48-53, 57-60, 62-65 and 80-85 are rejected under 35 U.S.C. 102(a) as being anticipated by Bot et al. (WO 00/00215).

Bot provides solid microparticle compositions (p. 25, lines 14-15 and p. 26, line 5). With regard to claims 1, 2, 6, 30, 37, 46, and 8 1-83, Bot teaches that the bioactive agent is encapsulated in a matrix (p. 9, line 11 to p. 10, line 16), and the matrix comprises a phospholipid (p. 2 1, lines 25-27), synthetic or natural polymers or combinations thereof, including albumin,

and disaccharides, such as lactose (p. 24, lines 3-25). Thus, Bot discloses pharmaceutical compositions comprising an agent encapsulated in a matrix comprising lipid, protein, sugar and synthetic polymer, as claimed in instant claims 2 and 81, or just lipid, protein (albumin) and sugar (lactose), as claimed in claims 1, 30, 37 and 46, or protein and sugar, as claimed in claim 6, or protein and synthetic polymer, as claimed in claim 82, or sugar and synthetic polymer, as claimed in claim 83.

With regard to claims 7, 13 and 20, the agent disclosed by Bot is a therapeutic protein and can be a vaccine, which is a prophylactic agent (p. 9, lines 1 1-28).

With respect to claims 18-20, 23-25, 27 and 28, the dipalmitoylphosphatidylcholle disclosed by the prior art (p. 21, lines 25-27 and p. 22, lines 18-29) is a naturally occurring phosphatidylcholine with no charge, an emulsifier and a surfactant, as claimed in claims 18-20, 23-25, 27 and 28 of the instant application.

Regarding claims 48-50, Bot teaches that the microparticles may comprise up to 100% of a surfactant, such as a phospholipid (p. 23, lines 18-26).

With regard to claims 51-53, Bot teaches that the microparticles may comprise up to 100% of bioactive agent (protein), and the protein can be in the matrix (p. 9, line 29 to p. 10, line 12).

With regard to claims 57-60 and 80, Bot provides particles having a size of 0.5-50 microns (p. 26, lines 11-23).

With regard to claims 62, 84 and 85, Bot teaches that the microparticles of the invention are formed by spray drying (p. 32, line 26 to p. 33, line 14).

Regarding claims 63-65, Bot teaches that the preparations may be administered by injection (p. 41, lines 2-5) and are delivered into body cavities (p. 40, lines 23-27).

The compositions disclosed by Bot meet the limitations of claims 1, 2, 6, 7, 13, 17-20, 23-25, 27, 28, 30, 37, 46, 48-53, 57-60 and 80-85, as the international publication contemplates pharmaceutical compositions comprising an active agent encapsulated in a matrix comprising lipid, protein, sugar and synthetic polymer, and methods of preparing and administering said compositions. Thus, Bot anticipates the claimed invention.

"When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

131-Declaration and the Bot Reference

Applicants insist that the evidence presented in the declaration of Dr. Kohane supports the claimed invention as solid microparticles encapsulated in a matrix and the nifedipine and bupivacaine are only examples merely representing to examples of agents.

4. Applicants' arguments filed 1/10/06 have been fully considered but they are not persuasive. Nifedipine and bupivacaine are narrower than the claimed agent in claim 1 and 9 and applicants may recite those specific drugs in the generic claim to overcome the art in terms of the date. Thus, the reference to nifedipne and bupivacaine in the declaration, Exhibit B of the declaration is not commensurate with the claimed scope of agents applicants are seeking protection. The scope of the declaration is not commensurate with the scope of the claims since the scope of the claims is broader and claim 1, for example, is directed to an agent encapsulated

in a matrix of lipid, protein and sugar; and exhibit B relates to encapsulating nifedipine and bupivacaine. Bot does not disclose liposomes.

5. The rejection of claims 63 and 64 under 35 U.S.C. 102(b) as being anticipated by Moynihan (US 5,589,189) is withdrawn in view of the amendment of claim 63 to exclude liposomes. .

Claim Rejections - 35 USC § 103

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 1, 2, 6, 7, 12-20, 23-25, 27, 28, 30, 37, 46-65 and 80-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345).

Applicants traverse the rejection on the basis that using Bernstein as art is an idea of picking and choosing, that Bernstein does no recognize that the various combinations of proteins, sugars, lipids and synthetic polymers can be used to formulate microparticles as the presently claimed invention recognizes, that examiner should point out the suggestion or teaching in Bernstein that preparation of such a composition would reasonably succeed in crating microparticles and that without such a showing a prima facie case of obvious ness has not been demonstrated.

8. Applicants' arguments filed 1/10/06 have been fully considered but they are not persuasive.

Regarding claims 6, 82 and 83, comprising language of the claims is open. While applicants have exclude lipid as part of the polymeric matrix, it is noted that in Bernstein, it is lipid or other hydrophobic or amphiphilic compound (abstract; column 1, lines63 and 64; column 2, lines 39-48; column 3, lines 32-67; column 4, lines 1-30). There is no picking and choosing and it is noted that claim 2 states "...at least three components selected form the group consisting of lipid, protein, sugar, and synthetic polymer" and claim 1 is directed to a matrix comprising lipid, protein and sugar. Thus in essence, more than one invention is claimed and a restriction/election between the various inventions is required. One invention has a matrix without lipid and the other invention has a matrix with lipid. Thus claims 6, 82 and 83 are distinct from claim 1. However, since in Bernstein lipid is optional for the matrix, the rejection is made.

Regarding a showing, applicants had the initial burden to show that the prima facie case is not tenable because when a rejection is made, the burden is on applicants to show that the claimed invention is not obvious over the prior art and applicants have no showing that preparing such a composition would not succeed. Excluding lipid from claims 6, 82 and 83 is not a showing. Bernstein discloses microparticles.

Bernstein discloses polymer matrices in the form of microparticles, wherein a lipid, or amphiphilic polymer or other hydrophobic compounds are integrated into polymeric matrix (abstract) and the matrix can be formed of synthetic or natural polymers, including proteins, such as albumin, and polysaccharides (sugars) and vasodilators (column 3, line 31 to column 4, line 22; column 6, line 56 to column 7 line 5).

Bernstein includes therapeutic and prophylactic agents among the active agents, which can be incorporated into the matrix (column 6, line 56 to column 7, line 5). The microparticles of Bernstein can be administered as powder, or formulated in tablets or capsules, or suspended in a solution with pharmaceutically acceptable carriers (column 9, lines 35-47).

The agents described in Bernstein are those that may be labeled with a fluorescent label or an enzymatic or chromatographically detectable agents (column 6, lines 61-63) are diagnostic agents. With respect to the amounts of lipid, protein and sugar claimed in claims 48-56 of the instant application, Bernstein teaches that the content of the lipid in the matrix is 0.01-60% in relation to the content of the polymer (column 6, lines 18-21) and the amount of polymer (protein) is 0.1-60% (column 4, lines 62-64). Therefore, the patent contemplates an amount of lipid up to 36%. With respect to the size of the claimed size of the microparticles claimed in claims 57-60 and 80 of the application, Bernstein discloses that the microparticles of the invention are manufactured with a diameter suitable for the intended route of administration, and discloses particles for intravascular administration having a diameter of 0.5 to 8 microns (column 2, lines 20-27). With regard to the particle size claimed in instant claim 61, Bernstein is deficient in the sense that the patent fails to disclose particles smaller than 0.5 microns. Applicant has not established comparable example in the specification to demonstrate that the claimed small size provides some unusual and/or unexpected results. It appears to the examiner that the smaller size of particles does nothing additional to the compositions of the invention, especially in view of the teachings of the prior art, that the microparticles of the invention can be administered by any route, including administration to the lungs (column 9, lines 56-63).

With respect to the method of preparing the microparticles claimed in claim 62,

Bernstein discloses that the microparticles of the invention can be produced by spray drying the polymer solution formed by dissolving the polymer (protein) and the lipid in the appropriate solvent, dispersing the active agent into the polymer solution (column 8, lines 18-33). With regard to the method of administering an agent claimed in claims 63-65 of the application, Bernstein discloses that the microparticles are combined with a pharmaceutically acceptable carrier and administered to a patient by injection into a blood vessel, subcutaneously, intramuscularly or orally (column 9, line 64 to column 10 line 6). Oral administration implies placing the microparticles in the oral cavity of the patient, thus the patent contemplates placing the microparticles in a body cavity of the patient, as claimed in claim 65 of the instant application. With respect to the ratio of lipid to protein to sugar claimed in claim 47 of the application, it is noted that applicants have no demonstration that the ratio of lipid claimed in the instant application provides unusual/unexpected results and there is no comparable example in the specification to demonstrate that the claimed ratio of lipid provides some unusual and/or unexpected results. It appears to the examiner that the higher ratio of lipid does nothing additional to the compositions of the invention, especially in view of the teachings of the prior art, that the hydrophobic compound integrated in the polymeric matrix modifies the diffusion of water into the microparticle and the diffusion of solubilized drug out of the matrix (column 2, lines 8-1 1).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Bernstein to prepare the microparticles of Bernstein with the expectation for controlled delivery of drugs.

9. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345) and further in view of Goldenheim et al. (US 6,534,081).

Applicants argue that the combination of Goldenheim and Bernstein cannot render the claims obvious because Bernstein does not teach the combination of lipid, protein, sugar and synthetic polymer.

10. Applicants' arguments filed 07/15/04 have been fully considered but they are not persuasive.

As stated above, "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose" and thus Bernstein disclose a composition that is obvious over the claims. Thus the combination of Goldenheim and Bernstein renders the claims obvious. Bernstein is discussed above.

The teachings of Bernstein et al. have been summarized above. The prior art is deficient in the fact, that it does not specifically include the anesthetics recited in claims 8-10 of the application and anticonvulsant agents, as claimed in claim 11, among the therapeutic agents encapsulated in the microparticles of the invention. Goldenheim provides sustained release dosage forms comprising a local anesthetic and an augmenting agent, and includes bupivacaine, dibucaine, tetracaine and lidocaine among the preferred local anesthetics used in the invention (column 3, line 50 to column 4, line 51). Goldenheim teaches that the local anesthetic is prepared in matrices of controlled release injectable microspheres (column 5, lines 60-64), and the formulations of the invention are suitable for administration in all body spaces and cavities (column 6, lines 55-59). Goldenheim discloses formulations comprising microparticles

comprising a local anesthetic, an augmenting agent and a sustained release polymer selected from synthetic polymers, proteins, polysaccharides and combinations thereof (column 7, lines 20-47). Thus, the patent provides the general teachings that local anesthetics can be delivered by microparticle compositions and specifically discloses the compounds recited in claims 8-10 of the instant application. With respect to claim 11, Goldenheim includes anticonvulsants among the augmenting agents incorporated in the compositions of the invention (column 12, lines 9-12).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Bernstein and the teachings of Goldenheim with the expectation of producing microparticles for the controlled delivery of local anesthetics and anticonvulsant drugs.

11. Claims 47, 54-56 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bot et al. (WO 00/00215).

The teachings of Bot have been summarized above. With regard to claims 47 and 54-56, Bot is deficient in the sense, that the prior art does not specifically disclose the ratio of lipid to protein to sugar and the amount of sugar in the matrix. It is the view of the examiner that the skilled artisan would have been able to determine the optimal ratio between the matrix components and amount of sugar by routine experimentation. With regard to claim 61, Bot fails to disclose particles smaller than 0.5 microns. Applicant has not established factual evidence that the small size of particles claimed in the instant application provides unexpected/unusual results and there is no comparable example in the specification to demonstrate that the claimed small size provides some unusual and/or unexpected results. It appears to the examiner that the smaller size of particles does nothing additional to the compositions of the invention, especially

in view of the teachings of the prior art, that the microparticles of the invention can be administered by any route, including inhalation (p. 41, lines 6-34).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the optimal ratio of lipid to protein to sugar and optimal amount of sugar in the matrix of the microparticles disclosed by Bot by routine experimentation to obtain pharmaceutical compositions having the desired release rate of the active agent encapsulated in the matrix with the expectation of desired drug delivery.

12. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bot et al. (WO 00/002 1 5) in view of Goldenheim et al. (U.S. Patent 6,534,08 1).

The teachings of Bot have been summarized above. The prior art is deficient in the fact that it does not specifically include the anesthetics recited in claims 8-10 of the application and anticonvulsant agents as claimed in claim 11, among the therapeutic agents encapsulated in the microparticles of the invention, and it does not teach microparticles having a diameter of less than 500 nanometers, as claimed in claim 61 of the instant application.

Goldenheim provides sustained release dosage forms comprising a local anesthetic and an augmenting agent, and includes bupivacaine, dibucaine, tetracaine and lidocaine among the preferred local anesthetics used in the invention (See col. 3, line 50 to col. 4, line 51). Goldenheim teaches that the local anesthetic is prepared in matrices of controlled release injectable microspheres (column 5, lines 60-64), and the formulations of the invention are suitable for administration in all body spaces and cavities (column 6, lines 55-59). Goldenheim discloses formulations comprising microparticles comprising a local anesthetic, an augmenting agent and a sustained release polymer selected from synthetic polymers, proteins,

polysaccharides and combinations thereof (column 7, lines 20-47). Thus, the patent provides the general teachings that local anesthetics can be delivered by microparticle compositions and specifically discloses the compounds recited in claims 8-10 of the instant application. With respect to claim 11, Goldenheim includes anticonvulsants among the augmenting agents incorporated in the compositions of the invention (column 12, lines 9-12).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Bot and the teachings of Goldenheim obtain microparticles that would be expected to controllably deliver local anesthetics and anticonvulsant drugs.

Response to Arguments

Regarding the rejections in paragraphs 11 and 12, applicants assert that:

a) Bernstein does not render obvious the matrix of the claimed invention having three components, and

b) The declaration by Dr. Kohane overcomes the rejection over Bot.

13. Applicants' arguments filed 1/10/06 have been fully considered but they are not persuasive.

a) As stated above, Bernstein discloses a composition that is obvious over the claims.

b) As stated above the declaration is not commensurate with the scope of the claims.

14. The rejection of claims 1, 2, 6, 7, 13, 16, 18-20, 23-25, 27, 28, 30, 37, 46 and 57-61 under 35 U.S.C. 103(a) as being unpatentable over Moynihan (US 5,589,189) is withdrawn in view of the amendment that excludes liposomes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 3:30 p.m. (Monday to Friday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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